UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,342	03/15/2004	Hyun Jin Hwang	12090-03USA	2316

7590 04/01/2008

JHK Law
P.O. Box 1078
La Canada, CA 91012-1078

EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
04/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/801,342	HWANG ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007 and 18 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-13,16,19,20,22-24,26 and 71-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13, 16, 19-20, 22-24, 26, 71-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 31, 2007 has been entered.

Claim Status

2. Supplemental amendment filed on January 18, 2008 is acknowledged. Claim set filed in this supplemental amendment will be examined in this action. Applicant has cancelled claims 1-7, 14-15, 17-18, 21, 25, 27-70; amended claims 8-12, 16, 19-20, 23, 26; added new claims 71-93. Currently claims 8-13, 16, 19-20, 22-24, 26, 71-93 are pending and will be examined in this action.

Priority

3. Applicant has submitted certified English translations of Korean applications filed on September 15, 2001 and October 30, 2001 respectively. Accordingly Applicant is entitled to the earlier priority going back to September 15, 2001 for the claims that find support in the PCT/KR02/01728 application filed on September 14, 2002. However for claims that find support only in the instant CIP application filed on March 15, 2004, the priority date still remains March 15, 2004.

Response to Claim Amendment

4. Applicant's arguments with respect to claims examined in previous office action have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended base claim 8 in a manner that broadens the scope of the claimed invention as well as imports a limitation of dependent claim 14 into the base claim. Since base claim 8 was rejected over Hunicke-Smith in view of Benett et al. and claim 14 was rejected over Hunicke-Smith; and Benett et al. as applied to claim 8 examined in previous office action, and further in view of Haff et al. Hence the rejection of base claim 8 over Hunicke-Smith; and Benett et al. is no longer applicable. Thus the rejections made in Office Action mailed on June 20, 2007 over previously cited art are withdrawn.

Regarding claim 8, the amendment deletes the limitation referring to shape of the reaction vessel and introduces the subject matter of claim 14 into base claim. As a result of deleting the limitation referring to shape of the reaction vessel the scope of the claimed invention broadens. Accordingly the cited art of Hunicke-Smith and Benett still apply. As indicated above, Haff et al. was used as secondary reference to teach the limitation of claim 14. Hence a rejection based on Hunicke-Smith; Benett et al. and Haff et al. covers all the elements of the amended claim 8.

Double Patenting Rejection

5. Applicant has not addressed the double patenting rejection that was made in the previous office action and thus it is also being maintained.

Claim Interpretation

6. Claims under prosecution are apparatus claims. All the independent claims have following section in them ---“ and wherein the spatial temperature distribution is a temperature distribution that induces circulation of the sample by thermal convection so that the denaturation, annealing, and polymerization steps occur sequentially and repeatedly inside the sample"----. The art cited by Examiner addresses the structural features recited in the claims. However the above section refers to how the apparatus functions and accordingly for prior art search purposes this section is not being considered any further as the functions recited are not associated with any specific structure of the apparatus that Examiner can search for. The art that is being cited teaches PCR machines that have high temperature zones in bottom and low temperature zones in top with liquid samples contained in the reaction vessel. When liquid is heated from bottom it rises and cold liquid from top comes down thus setting up circulation due to thermal convection within the liquid. So the scenario described will inherently occur in the samples provided the top temperature zone is cooler than the bottom temperature zone to which the sample is being subjected.

7. **NOTE** from Examiner: Applicant has added new claims that depend both from claim 8 and newly added claim 71 in this amendment. In order to keep the size of this office action reasonable, Examiner is rejecting base claim 8 once again over the new combination of references such that all the newly added dependent claims 71-90 can be rejected over this one set of references.

In addition Applicant has added two new independent claims 91 and 93 along with claim 92 that depends from claim 91. Though they are written as independent

claims, they contain features that are taught by art that is being cited below. Hence Examiner will not go into detail and just point out at the relevant art that teaches the main feature of claims 91-93.

Examiner is introducing a new piece of art (Wolfe et al.) that teaches the spatial arrangement of the plurality of heating/cooling sources with a layer of insulation positioned between them. All claims are being rejected over this art in view of the art cited that teaches the PCR apparatus described.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 8-12, 19-20, 22-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith WO 97/48818 published 24 December 1997 (cited by

applicant in the IDS) in view of Benett et al. WO 02/072267 A1 filed 22 February 2002 with US priority date of 9 March 2001 (cited by applicant in the IDS) and further in view of Haff et al. US.Pat. 5,720,923 issued February 24, 1998.

Regarding claim 8, Hunicke-Smith teaches:

A nucleic acid sequence amplification apparatus using PCR (see page 2, lines 5-6 where Hunicke-Smith teaches an apparatus for thermally cycling a DNA sample (another name used in the art for PCR is taught),

which apparatus comprises: a plurality of heat sources (see page 2, lines 6-7 where Hunicke-Smith teaches first and second heating elements)

which may supply heat to (see page 2, lines 7-12, where Hunicke-Smith teaches the heating chambers that contact the capillary tube containing sample),

or remove heat from (see page 3, lines 6-7, where Hunicke-Smith teaches a heating unit assembly further containing a cooling element that can remove heat from sample (contained in reaction vessel capillary in this case)).

Hunicke-Smith teaches selected first and second elevated temperature (page 2, lines 11-12).

Hunicke-Smith teaches "wherein the specific temperature distribution fulfilling a temperature condition suitable for (i) a denaturation step in which double strand DNAs become separated to single strand DNAs, (see page 2, lines 14-15, where Hunicke-Smith teaches temperature that is effective to denature the DNA sample) (ii) an annealing step in which the single strand DNAs formed in the denaturation step

hybridize to the primers to form DNA-primer complexes, or (iii) a polymerization step in which the primers in the DNA-primer complexes are extended by the polymerization reaction (see page 2, lines 15-16, where Hunicke-Smith teaches second temperature at which DNA annealing and primer directed DNA polymerization can occur).

Regarding claim 19, Hunicke-Smith teaches: wherein the plurality of heat sources (see page 2 lines 7-9, where first and second heating elements defining first and second heating chambers are taught) comprises a first thermally conductive solid that is in contact with a lower portion of the reaction vessel and a second thermally conductive solid that is in contact with an upper portion of the reaction vessel.(see Fig. 1A and page 7, lines 27-32 where heating unit assemblies are taught. Each heating unit assembly contains at least two heating elements, such as first heating element 24 that is in contact with a lower portion of sample(contained in capillary) and a second heating element 26 that is in contact with an upper portion of the sample (contained in capillary). The desired temperature in these heating elements is maintained by utilizing independently controlled heating elements, such as elements 24 and 26 using power transistors in integrated chips and microprocessors (see page 8, lines 13- 24). It is well known in the art that transistors and microprocessors on integrated chips are solids and the fact elements 24 and 26 serve as heating elements indicates they are de facto conductive solids. Thus Hunicke-Smith teaches thermally conductive solids.

Regarding claim 20, Hunicke-Smith teaches: The nucleic acid sequence amplification apparatus of claim 19, wherein the plurality of the heat sources further comprises a third thermally conductive solid that is in thermal contact with an

intermediate portion of the sample (contained in reaction vessel) in between the upper and lower portion. (see page 14, lines 4-10, where 3 separate heating chambers, formed by 3 separate heating elements and preferably containing 3 separate temperature sensors-one for each heating element are taught. They teach that the third chamber of each assembly provides a third temperature zone though which the DNA sample may be cycled thus accomplishing 3 temperature PCR employing a denaturing temperature (high temperature), an annealing temperature (low temperature) and an extension (intermediate temperature). It should be noted that Hunicke-Smith does not explicitly state that the third thermally conductive solid is in thermal contact with an intermediate portion of the reaction vessel in between the upper and lower portion. Fig. 5 shows 3 heating elements 110, 112, 114. But no reference is made about spatial temperature distribution i.e. intermediate temperature is the portion between the upper and lower portion.

B) Regarding claim 8 Hunicke-Smith does not teach spatial temperature distribution therefore following elements related to spatial temperature distribution in the claim are not taught by Hunicke-Smith: a plurality of specific regions in a sample contained in a reaction vessel, wherein the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region is located lower in height than a relatively low temperature region.

, and wherein the specific spatial temperature distribution is a temperature distribution that induces circulation of the sample by thermal convection so that the

denaturation, annealing, and polymerization steps occur sequentially and repeatedly inside the sample".

C) Regarding claim 8, Benett et al. teach:

a plurality of specific regions in a sample contained in a reaction vessel (see Fig. 3 where Benett et al. teach two sample regions marked 13 and 14 in a reaction vessel), wherein the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region is located lower in height than a relatively low temperature region (see page 5, lines 20-23 where Benett et al. teach a relatively high temperature region called the "Upper Temperature Zone 13" located lower in height than a relatively low temperature region called "Lower Temperature Zone 14". Bennett et al. teach that by heating specific sections a convection cell is created thereby necessarily teaching that the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region Zone 13 is located lower in height than a relatively low temperature region Zone 14.

In view of above teaching it is necessary that the intermediate temperature zone required for PCR extension will be a located in between the upper low temperature zone 14 and lower high temperature zone 13. Therefore clear description of spatial localization of high temperature zone to bottom and low temperature zone to top provides support to the conclusion that the intermediate temperature zone and the third

heating element recited in claim 20 and taught by Hunicke –Smith is actually located in a region in between the upper and lower portion.

Regarding claim 9, Benett et al. teach wherein at least one of the heat sources comprises a thermally conductive solid in thermal contact with a specific region of the reaction vessel or the sample (see page 5 line 23 where Benett et. al teach thermally conductive solid such as platinum heater as a heat source that is in contact with zone 13 of the reaction vessel; also see page 8, lines 11-14).

Regarding claim 22, Benett et al. teach *wherein the thermal convection is bidirectional.* (see Fig. 1. where bidirectional convection is shown flow of liquid is going one direction in channel 12a and flow of liquid in channel 12c is going in the other direction. Thus, Benett et al. teach *wherein the thermal convection is bidirectional.*

Regarding claim 26, Benett et al. teach the limitation of claim 22 above. The limitation wherein "the heat sources are further arranged to provide for a spatial temperature distribution comprising a convection region positioned between the relatively high temperature region and the relatively low temperature region". Since thermal convection taught in claim 22 by Benett et al., hence the required arrangement of heat sources recited in claim 26 is also taught by Benett et al.

It would have been prima facie obvious to one of ordinary skill in the art to combine the structural elements taught by Benett et al. in the PCR apparatus taught by Hunicke-Smith. The motivation to do so is provided by Benett et. al. who teaches the inefficiency associated with the conventional PCR machines where heating and cooling of material other than the PCR sample itself. They state "There is an increasing need to

build smaller more portable PCR systems for use in the field and clinical settings.---- This embodiment of the present invention provides a convectively driven PCR thermal-cycling system 10" (see Benett et. al. page 5, lines 7-14). Thus by combining the structural elements taught by Hunicke –Smith with the elements taught by Benett et. al. one would get a more efficient PCR apparatus that is capable of convective circulation thereby eliminating the cumbersome and contamination prone plunger system of moving the samples of Hunicke-Smith within the reaction vessel. Further Benett et al. point out that their system is also amenable to miniaturization as is intended by the applicant.

Regarding claim 8, neither Hunicke-Smith nor Benett et al. teach the limitation the apparatus further comprising an insulator positioned between the first and second heat sources.

Regarding claim 8, Haff et al. teach the apparatus further comprising an insulator positioned between the first and second heat sources.(see col. 7, lines 30-33 and Fig.1 where high temperature bath 16 and low temperature bath 18 are separated by a layer of insulation 20 which is selected to minimize the flow of heat between the two baths 16 and 18. Also see col. 15, lines 54-58 where layer of insulation 174 separating metal block heat exchangers 170 and 72 are taught).

Regarding claim 9, Haff et al. teach at least one of the heat sources comprises a thermally conductive solid in thermal contact with a specific region of the reaction vessel or the sample; and a heating unit that supplies heat to the thermally conductive solid (see col. 3, lines 66-67 and col 4, lines 1-3 where Haff et. al. teach two metal blocks

each of which has its temperature stabilized at one of two temperatures (denaturation and anneal/extend incubation) needed for PCR that are in thermal contact with the sample in the reaction vessel). Thus Haff et al. teach heat sources that are thermally conductive solid (metal blocks) in thermal contact with reaction vessel. By teaching blocks stabilized at temperatures required for PCR, a heating unit that supplies heat to these metal blocks is taught by Haff et al.

Regarding claims 10-11, Haff et al. teach wherein at least one of the heat source comprises a liquid in thermal contact with a specific region of the reaction vessel; a receptor in which the liquid is to be contained; and a heating unit that supplies heat to the liquid and wherein at least one of the heat sources further comprises a circulation unit that circulates the liquid around the reaction vessel. (see col. 3, lines 45-54 where Haff et al. teach use of two or three temperature stable fluid baths, each of which is constantly circulating its fluid through a separate conduit. Each fluid bath is thermostatted at one of the necessary PCR incubation temperatures (this teaching implies that the liquid in the bath is being heated by a heating unit and perhaps there is also a cooling unit that is helping to maintain the temperature required by the thermostat) this liquid of the fluid bath is in thermal contact with capillary (reaction vessel) containing the reaction mixture.)

Regarding claim 12, Haff et al. teach at least one of the heat sources comprises a gas in thermal contact with the reaction vessel; a heating unit that supplies heat to the gas and a circulation unit that circulates the gas around the reaction vessel. (see col. 2, lines 10-19, where an oven with a heating coil (source of heat), a solenoid activated

door and a fan (to circulate gas) are taught. Here Air was used as the heat transfer medium. The samples in capillary tubes are placed in this oven). Thus Haff et al. teach gas in thermal contact with the reaction vessel; a heating unit that supplies heat to the gas and a circulation unit that circulates the gas around the reaction vessel.

Regarding claim 23, Haff et al. teach wherein the insulator is a solid, liquid or a gas. (see col. 15, lines 54-58 where layer of insulation--insulator 174 separating metal block heat exchangers 170 and 72 are taught)

It would be prima facie obvious to one of ordinary skill in the art to combine the structural elements of the PCR apparatus taught by Haff et al. in the PCR apparatus taught by Hunicke-Smith and Benett et. al. The motivation to do so is provided by Haff et. al. because not only does Haff et. al. teach solid, liquid and gas sources of heat each of them having their own advantages as system of heat transfer but they also teach use of insulation between different heat sources as a means of insulating heat transfer between heating sources. In addition they teach use of Peltier device to control temperature of the metal blocks (see col. 16, lines 12-14), thereby allowing each heat source to efficiently maintain the desired temperature.

11. Claims 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith ; Benett et al. and Haff et al. as applied to claim 8 above, and further in view of Northup WO 98/25701 published 18 June 1998 (cited by applicant in the IDS).

Regarding claim 13, Hunicke-Smith ; Benett et al. and Haff et al. teach the PCR apparatus of claim 8 but do not teach wherein at least one of the heat sources is an infrared radiation generating unit that supplies heat directly to the sample.

Regarding claims 13, Northup teaches *wherein at least one of the heat sources is an infrared radiation generating unit that supplies heat directly to the sample* (see page 12, last 3 lines in bottom of page, where Northup teaches use of Infra Red (IR) source and Fig.3. where IR source 17 applies heat to solution in chamber 31.

It would be *prima facie* obvious to one of ordinary skill in the art to combine the structural elements of the PCR apparatus taught by Northup in the PCR apparatus taught by Hunicke-Smith ; Benett et al. and Haff et al.

The motivation to do so is provided by Northup who teach advantages associated with integrated microfabricated reactor developed for in situ chemical reactions, which is especially advantageous for biochemical reactions which require high precision thermal cycling, particularly DNA-base manipulations such as PCR, since small dimensions of microinstrumentation promote rapid cycling times (see page 4, par. 1).

12. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith, Benett et al. and Haff et al. as applied to claim 8 above, and further in view of Macho et al. US Pat. No. 5,919,622 issued July 6, 1999 (cited by applicant in the IDS).

Regarding claim 16, Hunicke-Smith, Benett et al. and Haff et al. teach the PCR apparatus of claim 8 but do not teach wherein heat source is shaped to comprise at least one protrusion that fits in an opening of the reaction vessel, wherein said protrusion contacts the sample.

Regarding claim 16, Macho et al. teaches wherein the heat source is shaped to comprise at least one protrusion that contacts the sample (see col. 5, lines 14-25 where

Macho et. al. teach a heat source that contacts the sample by dipping into the liquid contained in the vessel in a manner that the liquid receives an adequate amount of heat. Also see Fig 1. where protrusion 5 is shown to fit in an opening of the reaction vessel through stopper 3 with a lid 1 attached to it).

It would be prima facie obvious to one of ordinary skill in the art to combine the structural elements of the PCR apparatus taught by Macho et al. in the PCR apparatus taught by Hunicke-Smith; Benett et al. and Haff et al. The motivation to do so is provided by Macho et al. who state "The subject of the invention is a system for the temperature adjustment treatment of nucleic acid containing liquids in a vessel which has a reusable thermostat element and a disposable heating element, whereby heating element is a integral part of the vessel or the vessel lid and is dipped into the liquid during the treatment" see col. 2. lines 12-17. Also see col. 10 lines 63-64 where Macho et al. teach a heating element where the resistance wire extended about two thirds of the way into the PCR mix. Besides providing a source of heat, such a disposable arrangement also provides a means to selectively introduce a component such as polymerase into the reaction to start the reaction.

13. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith; Benett et al. and Haff et al. as applied to claim 23 above further in view of Bedingham et al. (U S Pat. 6,734,401 B2 filed on June 28, 2001).

Regarding claim 24, Hunicke-Smith; Benett et al. and Haff et al. teach the apparatus of claim 23, wherein insulating means is solid, liquid or a gas. Haff et al.

teach an insulating means but do not explicitly recite whether the insulating means is a solid, liquid or gas.

Regarding claim 24, Bedingham et al. teach wherein the insulating means is air (see col. 39 line 35 and line 60-61 where air is taught as insulating material).

It would have been prima facie obvious to one of ordinary skill in the art to combine the use of air as insulating means taught by Bedingham et al. in the PCR apparatus taught by Hunicke-Smith; Benett et al. and Haff et al. The motivation to do so is provided by Bedingham et al. who teach a device for thermal cycling that is useful for processing multiple samples simultaneously. The device uses electromagnetic energy to heat the base. Both the base plate and the device are rotated around an axis of rotation. In such a device air is used as insulating mean. Bedingham et al. state "Thermal isolation of a process chamber 1650 in the device can be enhanced by removing material around the process chamber 1650-------. Essentially, the process chamber 1650 is surrounded by one or more voids. Channels to deliver-----. Thermal isolation is improved by removing material around the ring 1652 that could serve as a heat sink, drawing thermal energy away from the process chamber 1650 during heating, or supplying stored thermal energy to the process chamber when cooling is desired" (see Bedingham et al. col. 39, lines 17-31).

14. Claims 8 and 71-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith WO 97/48818 published 24 December 1997 (cited by applicant in the IDS) in view of Benett et al. WO 02/072267 A1 filed 22 February 2002 with US priority date of 9 March 2001 (cited by applicant in the IDS); in view of Quintanar et al.

(US pat. 6,472186 issued October 29, 2002 with priority back to Jun 24, 1999) and further in view of Haff et al. US.Pat. 5,720,923 issued February 24, 1998.

Regarding claim 8, Hunicke-Smith teaches:

A nucleic acid sequence amplification apparatus using PCR (see page 2, lines 5-6 where Hunicke-Smith teaches an apparatus for thermally cycling a DNA sample (another name used in the art for PCR is taught),

which apparatus comprises: a plurality of heat sources (see page 2, lines 6-7 where Hunicke-Smith teaches first and second heating elements)

which may supply heat to (see page 2, lines 7-12, where Hunicke-Smith teaches the heating chambers that contact the capillary tube containing sample),

or remove heat from (see page 3, lines 6-7, where Hunicke-Smith teaches a heating unit assembly further containing a cooling element that can remove heat from sample (contained in reaction vessel capillary in this case)).

Hunicke-Smith teaches selected first and second elevated temperature (page 2, lines 11-12).

Hunicke-Smith teaches "wherein the specific temperature distribution fulfilling a temperature condition suitable for (i) a denaturation step in which double strand DNAs become separated to single strand DNAs, (see page 2, lines 14-15, where Hunicke-Smith teaches temperature that is effective to denature the DNA sample) (ii) an annealing step in which the single strand DNAs formed in the denaturation step hybridize to the primers to form DNA-primer complexes, or (iii) a polymerization step in

which the primers in the DNA-primer complexes are extended by the polymerization reaction (see page 2, lines 15-16, where Hunicke-Smith teaches second temperature at which DNA annealing and primer directed DNA polymerization can occur).

Regarding claim 75, Hunicke-Smith teaches wherein the opening further comprises a first through hole within the second heat source (see Fig. Fig. 1a and page 2, lines 9-10 where capillary is taught to pass through two heating chambers thus necessarily teaching the opening further comprises a first through hole within the second heat source) .

Regarding claim 8 Hunicke-Smith does not teach spatial temperature distribution therefore following elements related to spatial temperature distribution in the claim are not taught by Hunicke-Smith: a plurality of specific regions in a sample contained in a reaction vessel, wherein the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region is located lower in height than a relatively low temperature region.

, and wherein the specific spatial temperature distribution is a temperature distribution that induces circulation of the sample by thermal convection so that the denaturation, annealing, and polymerization steps occur sequentially and repeatedly inside the sample".

Regarding claim 8, Benett et al. teach:

a plurality of specific regions in a sample contained in a reaction vessel (see Fig. 3 where Benett et al. teach two sample regions marked 13 and 14 in a reaction vessel),

wherein the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region is located lower in height than a relatively low temperature region (see page 5, lines 20-23 where Benett et al. teach a relatively high temperature region called the "Upper Temperature Zone 13" located lower in height than a relatively low temperature region called "Lower Temperature Zone 14". Bennett et al. teach that by heating specific sections a convection cell is created thereby necessarily teaching that the heat sources are arranged to maintain a specific spatial temperature distribution in the sample such that a relatively high temperature region Zone 13 is located lower in height than a relatively low temperature region Zone 14.

In view of above teaching it is necessary that the intermediate temperature zone required for PCR extension will be a located in between the upper low temperature zone 14 and lower high temperature zone 13. Therefore clear description of spatial localization of high temperature zone to bottom and low temperature zone to top provides support to the conclusion that the intermediate temperature zone and the third heating element recited in claim 20 and taught by Hunicke –Smith is actually located in a region in between the upper and lower portion.

It would have been prima facie obvious to one of ordinary skill in the art to combine the structural elements taught by Benett et al. in the PCR apparatus taught by Hunicke-Smith. The motivation to do so is provided by Benett et. al. who teaches the inefficiency associated with the conventional PCR machines where heating and cooling of material other than the PCR sample itself. They state "There is an increasing need to

build smaller more portable PCR systems for use in the field and clinical settings.---- This embodiment of the present invention provides a convectively driven PCR thermal-cycling system 10" (see Benett et. al. page 5, lines 7-14). Thus by combining the structural elements taught by Hunicke –Smith with the elements taught by Benett et. al. one would get a more efficient PCR apparatus that is capable of convective circulation thereby eliminating the cumbersome and contamination prone plunger system of moving the samples of Hunicke-Smith within the reaction vessel. Further Benett et al. point out that their system is also amenable to miniaturization as is intended by the applicant.

Regarding claim 8, Quintanar et al. teach a high speed apparatus for amplifying DNA. The apparatus uses a plurality of heat sources (they use gases as plurality of heat sources (see Fig. 1 where plurality of gases such as helium are taught that can be used as heat sources)

which may supply heat to or remove heat from (see col. 6 lines 35-41 where gases such as helium, Carbon dioxide and air are taught as the gases that can be employed for rapid heating/ cooling of the reaction chamber).

Quintanar et al. teach that the heat chamber and reaction chamber are physically separated in space (see col. 6 lines 41-42) thus meeting the limitation that the heating /cooling gases are supplying heat to removing heat from the sample that is contained in the reaction chamber. (see Fig. 2B panel Pressurized Gas).

In one embodiment heated pressurized helium serves as heating source and cold pressurized CO_2 serves as cooling source (see col. 6 lines 66-67). The two gases are taught by Quintanar et al. are delivered to different regions of the reaction vessel (see Fig. 3c where valve 25 delivers hot pressurized gas to left side of reaction vessel and valve 26 delivers cold pressurized gas to right side of reaction vessel.

Regarding claim 71, Quintanar et al. teach wherein at least one of the heat sources comprises a heating unit and a cooling unit (see Fig. 3a where chamber 11 is heating unit and chamber 12 is shown as cooling unit--described in col. 6 lines 59-67. Thus teaching at least one of the heat sources comprises a heating unit and a cooling unit).

Regarding claim 72, Quintanar et al. teach wherein the second heat source comprises the heating and cooling units (pressurized heated or cold gases are taught as heating/cooling sources by Quintanar et al. see above. Further Fig. 1 lists at least 6 different gases. Therefore any of the desired combination of gases at different temperatures (comprising heating and cooling units) can be used. Thus Quintanar et al. teach wherein the second heat source comprises the heating and cooling units.

Regarding claim 73, Quintanar et al. teach wherein the apparatus further comprises an opening defined by the plurality of heat sources and the insulator, the opening being adapted to receive a reaction vessel with the sample (see Fig. 3a opening is shown in reaction chamber 23 that can be closed by cap 24.

Regarding claim 74, Quintanar et al. teach wherein the opening further comprises a closed bottom end within the first heat source. (see Fig. 9 where reaction chamber further comprises a closed bottom end within the first heat source).

Regarding claim 78, Quintanar et al. teach wherein the opening is configured to receive the reaction vessel configured as a straight cylinder or tube (see Fig. 9 where reaction chamber is shown to hold a straight cylinder or tube. Thus teaching wherein the opening is configured to receive the reaction vessel configured as a straight cylinder or tube).

Regarding claim 82, Quintanar et al. teach wherein the reaction vessel is pressurized (see col. 5 lines 4-8 where delivery of pressurized gas to reaction chamber is taught).

Regarding claim 83, Quintanar et al. teach wherein the reaction vessel comprises a top end and a bottom end (see Fig. 3a where reaction chamber is shown to have a top closable hole and see fig. 9 where the reaction vessel inside the chamber is shown to have a top and a bottom end).

Regarding claim 84, Quintanar et al. teach wherein the reaction vessel is tapered. (see Fig. 9 where the sample tube shown is tapered)

Regarding claim 85, Quintanar et al. teach wherein the reaction vessel is tapered from the top end to the bottom end (tube shown in fig. 9 is tapered from the top end to the bottom end).

Regarding claim 86, Quintanar et al. teach wherein the reaction vessel is tapered from the bottom end to the top end. (Quintanar et al. teach a reaction chamber 23 with a

cavity inside which has a closable opening 24. Into this cavity reaction vessel of any desired shape can be placed as desired. Erlenmeyer flask, used in the molecular biology laboratories is a reaction vessel that is tapered from the bottom end to the top end. See MPEP 2144.06 Art Recognized Equivalence for the Same Purpose [R-6]. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious.

Regarding claim 87, Quintanar et al. teach wherein the bottom end of the reaction vessel is closed (as described for claim 86 above the Erlenmeyer flask or eppendorf tubes used in molecular biology will be examples of reaction vessels wherein the bottom end of the reaction vessel is closed). See MPEP 2144.06 Art Recognized Equivalence for the Same Purpose [R-6]. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious.

Regarding claim 90, Quintanar et al. teach wherein the apparatus further comprises a gap between the reaction vessel and at least the second heat source (see fig. 9 where reaction vessel is contained in a reaction chamber which in turn is separated from the heat sources. Thus Quintanar et al. teach wherein the apparatus further comprises a gap between the reaction vessel and at least the second heat source).

It would have been prima facie obvious to one of ordinary skill in the art to combine the gas heated/cooled PCR apparatus taught by Qunitanar et al. into the PCR apparatus of Hunicke-Smith and Benett et al. at the time the invention was made. The motivation to do so is provided by Quintanar et al. who state " A novel process, high speed gas phase PCR, is described. This process has been successfully automated using a novel thermocycling device, which has been successfully to amplify DNA from picogram to microgram amounts in ~1 to 5 minutes." (see last part of abstract). So one would have a miniature PCR apparatus as taught by Benett et al. and this miniature PCR apparatus would be fast as well as taught by Quintanar et al.

Regarding claim 8, Quintanar et al. also teach an insulating material that separates the reaction chamber (element 23 of Fig. 3a) from the heating and cooling chambers (col. 8 lines 48-59). Since three separate chambers (heating, cooling and reaction chambers are taught by Quintanar et al. they are each separated from each other hence are insulated from each other by air. However, the location of the heating and cooling chambers is not adjacent to meet the limitation recited in last part of claim namely insulator positioned between the first and second heat sources.

Thus regarding claim 8, neither Hunicke-Smith nor Benett et al. or Quintanar et al. teach the limitation the apparatus further comprising an insulator positioned between the first and second heat sources.

Regarding claim 8, Haff et al. teach the apparatus further comprising an insulator positioned between the first and second heat sources.(see col. 7, lines 30-33 and Fig.1 where high temperature bath 16 and low temperature bath 18 are separated by a layer of insulation 20 which is selected to minimize the flow of heat between the two baths 16 and 18. Also see col. 15, lines 54-58 where layer of insulation 174 separating metal block heat exchangers 170 and 72 are taught).

Regarding claim 76, Haff et al. teach wherein the opening further comprises a second through hole within the insulator (see col. 16 lines 30-34 where reaction capillary tube is taught to pass through two metal block heat exchangers 170 and 172. The insulator 174 is present between the two blocks (see above). Hence the opening of reaction vessel taught by Haff et al. necessarily further comprises a second through hole within the insulator else the capillary tube could not pass through the two blocks 170 and 172 that have insulator 174 in between them.

Regarding claim 77, Haff et al. teach wherein the opening is essentially perpendicular to the insulator (as described in claim 76 above the arrangement heat block bottom, insulator and heat block top with hole through them to hold the capillary essentially indicates that the opening is essentially perpendicular to the insulator) .

Regarding claim 79, Haff et al. teach wherein the reaction vessel is further configured to have a single passage between the relatively high temperature region and

the relatively low temperature region (see above for claims 76 and 77 where capillary is taught to fit in the hole that passes through the two metal blocks separated by insulator. The reaction vessel --capillary tube in this case necessarily has a single passage between the relatively high temperature region and the relatively low temperature region—the two metal blocks at high and low temperatures).

Regarding claim 80, Haff et al. teach wherein the single passage is adapted to contain an upward and downward convective flow. (Applicant has not provided any structural limitation in the instant claims as to how the single passage has to be adapted to contain an upward and downward convective flow. See claim 79 above where Haff et al. teach the reaction vessel that has a single passage between the relatively high temperature region and the relatively low temperature region. A reaction tube or vessel containing a single passage is inherently capable of containing an upward and downward convective flow. Therefore Haff et al. teach the single passage is adapted to contain an upward and downward convective flow.)

Regarding claim 81, Haff et al. teach wherein the reaction vessel is vertical with respect to the heat sources. (see claim 76 and 77 above the arrangement of the heat blocks—heat sources and the holes through them necessarily indicate that the reaction vessel (capillary tube) is vertical with respect to the heat sources.

Regarding claim 88, Haff et al. teach wherein the apparatus further comprises multiple reaction vessels (see col. 4 line 5 where plurality of capillary tubes are taught. Thus teaching multiple reaction vessels).

Regarding claim 89, Haff et al. teach wherein the plurality of heat sources are further arranged to produce a vertical gap between the top of the relatively high temperature region and the bottom of the relatively low temperature region (see above for claims 8 and 76, where Haff et al. teach an insulator between the top of the a high temperature region (heat block) on bottom and the bottom of the relatively low temperature region (heat block). Haff et al. do not spell out what is the nature of the insulation used. In view of the broad teaching of insulation located between the two heat sources. One of ordinary skill in the art might envisage using any suitable insulator such as air as a layer of insulation between the bottom and top heat source. In such an embodiment we would have following arrangement --- bottom high temp heat block air as an insulator in the space over the bottom block and top low temp heat block. This would result in an identical arrangement as recited in the instant claim. Thus by broad teaching of insulator—Haff et al. teach use of air as an insulator and hence teach to one of ordinary skill wherein the plurality of heat sources are further arranged to produce a vertical gap between the top of the relatively high temperature region and the bottom of the relatively low temperature region).

It would be prima facie obvious to one of ordinary skill in the art to combine the structural elements of the PCR apparatus taught by Haff et al. in the PCR apparatus taught by Hunicke-Smith; Benett et al. and Quintanar et al. The motivation to do so is provided by Haff et al. because not only does Haff et al. teach solid, liquid and gas sources of heat each of them having their own advantages as system of heat transfer but they also teach use of insulation between different heat sources as a means of

insulating heat transfer between heating sources. In addition they teach use of Peltier device to control temperature of the metal blocks (see col. 16, lines 12-14), thereby allowing each heat source to efficiently maintain the desired temperature.

15. Claims 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith WO 97/48818 published 24 December 1997 (cited by applicant in the IDS) in view of Benett et al. WO 02/072267 A1 filed 22 February 2002 with US priority date of 9 March 2001 (cited by applicant in the IDS); in view of Quintanar et al. (US pat. 6,472186 issued October 29, 2002 with priority back to Jun 24, 1999) and further in view of Haff et al. US.Pat. 5,720,923 issued February 24, 1998.

Regarding claim 91, a nucleic acid sequence amplification apparatus using PCR, which apparatus comprises:

a plurality of heat sources which supply heat to, or remove heat from a plurality of specific regions within an opening configured to receive a reaction vessel (Hunicke-Smith cited above teaches this) and defined by the plurality of heat sources (Hunicke-Smith, Benett et al., Quintanar et al. and Haff et al. all cited above all of them teach this) and an insulator (Haff et al. teaches this),

wherein the plurality of heat sources are arranged to maintain a spatial temperature distribution within the opening such that a first heat source providing heat to a lower portion of the opening is located lower in height than a second heat source removing heat from an upper portion of the opening and a relatively high temperature region is located lower in height than a relatively low temperature region in the opening, wherein the spatial temperature distribution comprises spatial regions fulfilling

temperature conditions suitable for (i) a denaturation step in which double strand DNAs become separated to single strand DNAs, (ii) an annealing step in which the single strand DNAs formed in the denaturation step hybridize to the primers to form DNA-primer complexes, or (iii) a polymerization step in which the primers in the DNA-primer complexes are extended by the polymerization reaction,

and wherein the spatial temperature distribution is a temperature distribution that induces circulation of sample by thermal convection so that the denaturation, annealing, and polymerization steps occur sequentially and repeatedly inside the sample (see the section on claim interpretation above),

the insulator being positioned between the first and second heat sources and in contact with the opening (see Haff et al. as described above),

and further wherein at least one of the heat sources comprises a heating unit and a cooling unit. (see details of claim 8 rejection above for this) .

Regarding claim 92, wherein the opening further comprises a closed bottom end within the first heat source (Quintanar et al. et al. teach opening further comprises a closed bottom end within the first heat source. See above).

16. Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hunicke-Smith WO 97/48818 published 24 December 1997 (cited by applicant in the IDS) in view of Benett et al. WO 02/072267 A1 filed 22 February 2002 with US priority date of 9 March 2001 (cited by applicant in the IDS); in view of Quintanar et al. (US pat. 6,472186 issued October 29, 2002 with priority back to Jun 24, 1999) and further in view of Haff et al. US.Pat. 5,720,923 issued February 24, 1998.

Regarding claim 93, a nucleic acid sequence amplification apparatus using PCR, which apparatus comprises:

a plurality of heat sources which supply heat to, or remove heat from a plurality of specific regions in a sample,

wherein the plurality of heat sources are arranged to maintain a spatial temperature distribution in the sample such that a first heat source providing heat to a lower portion of the sample is located lower in height than a second heat source removing heat from an upper portion of the sample and a relatively high temperature region is located lower in height than a relatively low temperature region in the sample, wherein the spatial temperature distribution comprises spatial regions fulfilling temperature conditions suitable for (i) a denaturation step in which double strand DNAs become separated to single strand DNAs, (ii) an annealing step in which the single strand DNAs formed in the denaturation step hybridize to the primers to form DNA-primer complexes, or (iii) a polymerization step in which the primers in the DNA-primer complexes are extended by the polymerization reaction, and wherein the spatial temperature distribution is a temperature distribution that induces circulation of the sample by thermal convection so that the denaturation, annealing, and polymerization steps occur sequentially and repeatedly inside the sample, and further wherein at least one of the heat sources comprises a heating unit and a cooling unit.

All the elements of this claim have been discussed above.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 8, 16 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 8 of copending Application No. 10/836,376. Although the conflicting claims are not identical, they are not patentably distinct from each other because the PCR apparatus described in claims 7 and 8 of copending application make the PCR apparatus claimed in claims 8, 16 and 20 of the instant application obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

19. All claims 8-13, 16, 19-20, 22-24, 26, 71-93 under consideration are rejected over prior art. Examiner has purposefully added the rejection over Wolfe et al. to illustrate to applicant that they need to narrow the claims by introducing structural limitations that distinguish their apparatus over prior art. The currently recited claims do not distinguish the invention over the existing prior art.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637

March 26, 2008